



Clinical characteristics of patients with anti-aminoacyl-tRNA synthetase antibody positive idiopathic interstitial pneumonia

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ABSTRACT

Background: Anti-aminoacyl-tRNA synthetase (ARS) antibodies have been detected in patients with polymyositis/dermatomyositis (PM/DM) and are especially correlated with interstitial lung disease (ILD). The aim of this study was to clarify the clinical features of patients with anti-ARS antibody positive idiopathic interstitial pneumonias (IIPs).

Methods: Patients were classified into three groups: 1) IIP with anti-ARS antibodies (ARS(+)IIP), 2) IIP without anti-ARS antibodies (ARS(−)IIP), and 3) PM/DM-associated ILD with anti-ARS antibodies (ARS(+)PM/DM-ILD). Clinical characteristics were compared retrospectively between the ARS(+)IIP group and the ARS(−)IIP group or ARS(+)PM/DM-ILD group.

Results: Eighteen ARS(+)IIP, 284 ARS(−)IIP, and 20 ARS(+)PM/DM-ILD patients were enrolled. The ARS(+)IIP group was significantly older and the male sex was predominant, had a lower prevalence of signs of connective tissue disease, differences in HRCT findings and patterns, and higher KL-6 levels compared to the ARS(+)PM/DM-ILD group. The findings in the bronchoalveolar lavage fluid (BALF) showing lymphocytosis and a lower CD4/CD8 ratio were similar between the two groups. However, the ARS(+)IIP group had significantly lower percentage of sputum, higher prevalence of mechanic's hand, higher KL-6 levels, lower percentage of vital capacity in the pulmonary function test, and lower CD4/CD8 ratio in BALF, compared to the ARS(−)IIP group.

Conclusions: The present study demonstrated that features of pulmonary involvement were similar to those in the ARS(+)PM/DM-ILD group; however, some differences including HRCT findings and higher KL-6 levels suggest that ARS(+)IIP has severe ILD compared with ARS(+)PM/DM-ILD. Further prospective studies with a larger number of patients will elucidate the exact role of anti-ARS antibodies in IIPs.

Abbreviations: ALD, aldolase; ARS, anti-aminoacyl-tRNA synthetase; ARS(−), anti-ARS antibody negative; ARS(+), anti-ARS antibody positive; ASS, anti-synthetase syndrome; BALF, bronchoalveolar lavage fluid; CADM, clinically amyopathic dermatomyositis; CK, creatine kinase; CT, computed tomography; CTD, connective tissue diseases; DAD, diffuse alveolar damage; HRCT, high-resolution computed tomography; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen 6; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; PM/DM, polymyositis/dermatomyositis; UIP, usual interstitial pneumonia; %VC, percentage of the vital capacity

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1. Introduction

Idiopathic interstitial pneumonias (IIPs) are diagnosed based on the involvement of the lung parenchyma with varying combinations of fibrosis and inflammation and exclusion of known causes of interstitial pneumonia, such as connective tissue diseases (CTD) [1,2]. Patients with IIP occasionally have clinical features that suggest an underlying autoimmune disease without meeting current criteria for the diagnosis of a particular CTD. This subset of interstitial lung diseases (ILD) has been classified into categories such as undifferentiated CTD-associated ILD [3], lung-dominant CTD [4], autoimmune-featured ILD [5], and interstitial pneumonia with autoimmune features (IPAF) [6].

Anti-aminoacyl-tRNA synthetase (ARS) antibodies that recognize cytoplasmic ARS are known as the most common myositis-specific antibodies detected in polymyositis/dermatomyositis (PM/DM). Eight anti-ARS antibodies have been identified thus far: anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-KS, anti-Zo, and anti-Ha. PM/DM patients can be classified into subsets based on myositis-specific antibodies that are associated with clinically common features [7,8]. Patients with anti-ARS antibodies are associated with a unique subset of features characterized by inflammatory myopathy, arthritis, Raynaud's phenomenon, mechanic's hands, and ILD, called anti-synthetase syndrome (ASS) [9,10]. Although anti-ARS has been described mainly in PM/DM, detection of anti-ARS antibodies in rheumatoid arthritis or IIPs without myositis have also been reported [11–14]. Nevertheless, most studies on anti-ARS were performed in patients with PM/DM and the clinical characteristics of IIPs with anti-ARS antibodies are still unclear. The aim of this study was to clarify the clinical characteristics of patients with anti-ARS antibody positive IIPs by comparing those with IIPs without anti-ARS antibodies or PM/DM-ILD with anti-ARS antibodies.

2. Material and methods

2.1. Study population

Consecutive Japanese patients with IIP who visited the Department of Respiratory Medicine at Nagasaki University Hospital and the Hospital of the University of Occupational and Environmental Health and Japanese patients with PM/DM associated ILD (PM/DM-ILD) who visited the Department of Respiratory Medicine at Nagasaki University Hospital from 2008 to 2015, were retrospectively studied. The diagnosis of IIP was based on the clinical presentation during the first visit to our hospitals. IIP was defined as interstitial pneumonia of unknown cause where the patient did not fulfill classification criteria for any specific CTD or vasculitis. Lung diseases that were potentially caused by drug or occupational-environmental exposures were also excluded [1,2]. A clinical diagnosis of PM/DM was made according to Bohan and Peter's criteria [15,16]. A diagnosis of clinically amyopathic dermatomyositis (CADM) was made when a patient had typical skin manifestations such as Gottron's sign and a heliotrope rash without muscle symptoms and an elevation of serum myogenic enzymes during the observation period [17–19]. Patients were classified into three groups in this study. Patients with IIP were classified into the anti-ARS antibody positive (ARS(+))IIP or negative (ARS(–))IIP groups and anti-ARS antibody positive patients with PM/DM were defined as the ARS(+))PM/DM-ILD group. None of the patients with IIP with anti-ARS antibodies developed any additional finding of connective tissue disease during the observation period. Blood samples were collected from each patient during the primary visit and stored at -20°C until use. For the anti-ARS antibody analysis, sera were analyzed by immunoprecipitation of ^{35}S -methionine-labeled K562 cell extract; specificities of autoantibodies were determined by using specific reference sera [20].

All demographic and clinical information was obtained retrospectively from medical records at the time of the initial diagnosis. Acute exacerbation was defined as follows: 1) a previous or concurrent

diagnosis of interstitial pneumonia, 2) acute worsening or development of dyspnea of typically < 1 month in duration, 3) computed tomography (CT) with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern, and 4) deterioration not fully explained by cardiac failure or fluid overload [21].

The study protocol was approved by the Human Ethics Review Committee at Nagasaki University School of Medicine and the Hospital of the University of Occupational and Environmental Health, Japan. A signed informed consent was obtained from all subjects in accordance with the Declaration of Helsinki and its subsequent modifications.

2.2. Evaluation of high-resolution computed tomography (HRCT) findings and patterns

Chest HRCT of all patients was retrospectively assessed by two pulmonologists (N.S. and H.I.). The pulmonologists recorded the following features seen on HRCT: the distribution and presence of reticulation, honeycombing, traction bronchiectasis, ground-glass attenuation, consolidation, thickening of bronchovascular bundles, small nodules, and pleural effusion. The HRCT patterns were classified according to the international classification of IIPs created by the American Thoracic Society/European Respiratory Society [2]. HRCT patterns included usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), and diffuse alveolar damage (DAD). The classification of “others” was used when an HRCT finding did not meet the above patterns.

2.3. Statistical analysis

All values are expressed as medians (interquartile range) or the frequency (number). To clarify the characteristics of ARS(+))IIP group, differences between the ARS(+))IIP group and ARS(–))IIP group or ARS(+))PM/DM-ILD group were compared using the chi-squared test, Fisher's exact test, or the Steel test. Multiple pairwise group comparisons were performed to adjust the P value by using the Steel test or the Bonferroni correction for Fisher's exact test. In the Steel test, we set the ARS(+))IIP group as the investigated group and set the ARS(–))IIP and ARS(+))PM/DM-ILD groups as the control groups. Kaplan-Meier survival curves were constructed for the three group populations and comparisons were made using the log-rank test. A P value < 0.05 was regarded as statistically significant. All data were analyzed using JMP® Pro 11.2.0 (SAS Institute Inc., Cary, NC, USA).

3. Results

Three hundred and two consecutive Japanese patients with IIP who visited the Department of Respiratory Medicine at Nagasaki University Hospital or the Hospital of the University of Occupational and Environmental Health from 2008 to 2015 and 37 Japanese patients with PM/DM-ILD who visited the Department of Respiratory Medicine at Nagasaki University Hospital from 2008 to 2015, were enrolled.

3.1. Prevalence of anti-ARS antibodies

Anti-ARS antibodies were found in 18 (6.0%) of 302 patients with IIPs and in 20 (54.1%) of 37 patients with PM/DM-ILD. The specificities of the anti-ARS antibodies found in ARS(+))IIPs and ARS(+))PM/DM-ILD are shown in Table 1. Anti-Jo-1 was the most frequent antibody in both the ARS(+))IIP (N = 5, 27.8%) and ARS(+))PM/DM-ILD (N = 9, 45.0%) groups. Anti-KS was as common as the anti-Jo-1 antibody (N = 5, 27.8%) and anti-EJ antibody was detected in four patients (22.2%) in the ARS(+))IIP group. In the ARS(+))PM/DM-ILD group, anti-PL-7 antibody (N = 4, 20.0%) was the second most common antibody detected. The difference in the fine specificity of anti-ARS antibodies between these two groups was not significantly different (P = 0.581 by Fisher's exact test). Seven of 18 patients of ARS(+))IIP

Table 1
The types of each anti-ARS antibody.

	ARS(+)IIP		ARS(+)PM/DM-ILD	
	N = 18	(%)	N = 20	(%)
Jo-1	5	(27.8)	9	(45.0)
KS	5	(27.8)	2	(10.0)
EJ	4	(22.2)	2	(10.0)
PL-7	2	(11.1)	4	(20.0)
PL-12	1	(5.6)	1	(5.0)
OJ	1	(5.6)	2	(10.0)

IIP; idiopathic interstitial pneumonia.

PM/DM-ILD; polymyositis/dermatomyositis-interstitial lung disease.

had coexisting autoantibodies (three had the Rheumatoid factor, two the anti-cyclic citrullinated peptide antibody, one the anti-SS-A/Ro antibody, and one the anti-double stranded DNA antibody) without satisfying the classification criteria for other established rheumatic conditions. Twelve of 18 patients with ARS(+)IIP met the criteria of IPAF [6].

3.2. Clinical characteristics, symptoms, and physical findings

The demographic and clinical characteristics of the patients in the present study are summarized in Table 2. Patients in the ARS(+)IIP group were older than those in the ARS(+)PM/DM-ILD group (64.0 years vs. 58.5 years, $P = 0.030$ by the Steel test), but not significantly different from those in the ARS(−)IIP group (64.0 years vs. 70.0 years, $P = 0.082$). The ARS(+)IIP group showed a greater men predominance than the ARS(+)PM/DM-ILD group ($P = 0.038$). Sputum recorded as a respiratory symptom was less frequent in the ARS(+)IIP group than that in the ARS(−)IIP group ($P = 0.032$). Muscle weakness and arthritis were significantly less in the ARS(+)IIP group than in the ARS(+)PM/DM-ILD group ($P = 0.001$ and $P = 0.016$, respectively). Although patients in the ARS(+)IIP group did not fulfill the diagnostic criteria for PM/DM, mechanic's hand was more prevalent than in the ARS(−)IIP group, but less prevalent than in the ARS(+)PM/DM-ILD group ($P = 0.020$ and $P = 0.010$, respectively). Although the prevalence of Raynaud's phenomenon in the ARS(+)PM/DM-ILD group was high, it did not significantly differ from that in the ARS(−)IIP

Table 2
Clinical characteristics at initial presentation.

		ARS(−)IIP (N = 284)			ARS(+)IIP (N = 18)			ARS(+)PM/DM-ILD (N = 20)		
		% or No.	(IQR)	[n]	% or No.	(IQR)	[n]	% or No.	(IQR)	[n]
Patient characteristics										
Age (years)		70	(63–75)	[284]	64†	(60–75)	[18]	58.5	(50–62)	[20]
Gender	Men/Women	191/93		[284]	11/7†		[18]	4/16		[20]
Smoking	Current/Ex/Never	36/147/87		[270]	1/10/5		[16]	2/4/14		[20]
	B.I. (median)	440	(0–994)	[270]	200	(0–1200)	[16]	0	(0–320)	[20]
Dust exposure (%)		40.5		[220]	16.7		[12]	33.3		[9]
Respiratory symptoms										
Cough (%)		59.7		[273]	64.7		[17]	73.3		[15]
Sputum (%)		24.1		[270]	0*		[17]	7.1		[14]
Dyspnea (%)		67.4		[258]	83.3		[18]	86.7		[15]
Signs of connective tissue disease										
Muscle weakness (%)		0.7		[282]	0.0†		[18]	50.0		[20]
Raynaud's phenomenon (%)		2.5		[280]	5.6		[18]	31.6		[19]
Mechanic's hands (%)		0.4		[279]	11.1*†		[18]	57.9		[19]
Fever (%)		19.2		[282]	16.7		[18]	26.3		[19]
Arthritis/Joint stiffness (%)		5.0		[281]	5.6†		[18]	47.4		[19]

IQR; inter-quartile range, B.I.; Brinkman index.

*; p value < 0.05 between ARS(+)IIP and ARS(−)IIP.

†; p value < 0.05 between ARS(+)IIP and ARS(+)PM/DM-ILD.

Table 3
HRCT findings at initial presentation.

	ARS(−)IIP	ARS(+)IIP	ARS(+)PM/DM-ILD
	(N = 284)	(N = 18)	(N = 20)
Lower distribution (%)	67.6	94.4	100
Subpleural distribution (%)	69.5	61.1	35.0
Peribronchial distribution (%)	12.8	22.2	0.0
Reticulation (%)	83.7	94.4	75.0
Honeycombing (%)	39.4	22.2	0.0
Traction bronchiectasis (%)	78.0	94.4	90.0
Ground-glass attenuation (%)	69.9	72.2†	100.0
Consolidation (%)	30.9	33.3†	75.0
Thickening of BVB (%)	2.1	5.6	0.0
Small nodules (ϕ < 5 mm) (%)	7.2	0.0	0.0
Pleural effusion (%)	5.0	5.6	10.0

BVB; bronchovascular bundles.

†; p value < 0.05 between ARS(+)IIP and ARS(+)PM/DM-ILD.

($P = 0.792$) and ARS(+)PM/DM-ILD ($P = 0.179$) groups.”.

3.3. HRCT findings and patterns

Table 3 shows the HRCT findings in each group. By comparison of ARS(+)IIP vs ARS(+)PM/DM, ground-glass attenuation and consolidation were less frequently observed in the former group than in the latter ($P = 0.034$ and $P = 0.042$, respectively). Honeycombing was more common in the ARS(+)IIP group, found in 22.2% of patients while it was not found in the ARS(+)PM/DM-ILD group ($P = 0.042$). Other findings such as a lower distribution of abnormal findings and traction bronchiectasis were common in both the ARS(+)IIP and ARS(+)PM/DM-ILD groups. Table 4 summarizes the prevalence of HRCT patterns in each group. A UIP pattern, which represents clinical idiopathic pulmonary fibrosis (IPF), was the most frequent pattern in patients in the ARS(−)IIP group; NSIP was the second most frequent. In contrast, NSIP was the most frequent pattern in patients with ARS(+)IIP and ARS(+)PM/DM-ILD groups. The second most frequent HRCT pattern in the ARS(+)IIP group was UIP, while it was OP in the ARS(+)PM/DM-ILD group. A DAD pattern was also observed in patients in the ARS(+)IIP group. HRCT patterns in the ARS(+)IIP group were

Table 4
HRCCT patterns at initial presentation.

	ARS(–)IIP		ARS(+)IIP [†]		ARS(+)PM/DM-ILD	
	N = 281	(%)	N = 18	(%)	N = 20	(%)
UIP	118	(42.0)	4	(22.2)	0	(0.0)
NSIP	85	(30.3)	10	(55.6)	17	(85.0)
OP	33	(11.7)	0	(0.0)	3	(15.0)
DAD	9	(3.2)	2	(11.1)	0	(0.0)
others	36	(12.8)	2	(11.1)	0	(0.0)

UIP; usual interstitial pneumonia, NSIP; nonspecific interstitial pneumonia.

OP; organizing pneumonia, DAD; diffuse alveolar damage.

Others; not conform to any of described patterns.

†; p value < 0.05 between ARS(+)IIP and ARS(+)PM/DM-ILD.

significantly different from those in the ARS(+)PM/DM-ILD group (P = 0.002 by Fisher's exact test).

3.4. Laboratory data, pulmonary function test, and BALF findings

Table 5 shows the results of the laboratory findings at the initial presentation. Serum Krebs von den Lungen 6 (KL-6) levels were significantly higher in the ARS(+)IIP group compared with both the ARS(–)IIP group and the ARS(+)PM/DM-ILD group (P = 0.007 and P = 0.021, respectively). The pulmonary function test showed that the percentage of the vital capacity (%VC) in the ARS(+)IIP group was the lowest among the three groups and there was a significant difference between the ARS(+)IIP and ARS(–)IIP groups (P = 0.030). BALF cell analysis in the ARS(+)IIP group showed a higher percentage of lymphocytes and lower CD4/CD8 ratios. There was a significant difference in CD4/CD8 ratios between the ARS(+)IIP group and the ARS(–)IIP group (P = 0.002), but not between the ARS(+)IIP group and the ARS(+)PM/DM-ILD group (P = 0.999).

3.5. Clinical course

Table 6 summarizes the clinical courses of patients in each group.

Table 5
Laboratory data, pulmonary function test and BALF findings at initial presentation.

	ARS(–)IIP			ARS(+)IIP			ARS(+)PM/DM-ILD		
		(IQR)	[n]		(IQR)	[n]		(IQR)	[n]
Laboratory data									
CRP (mg/dL)	0.48	(0.12–2.68)	[274]	0.35	(0.15–3.86)	[18]	0.25	(0.06–1.15)	[20]
AST (IU/L)	24.0	(19.0–30.0)	[277]	22.0	(19.0–28.5)	[17]	34.0	(21.5–61.0)	[20]
LDH (IU/L)	226	(193.0–285.3)	[274]	255.5	(192.5–358.0)	[17]	312.5	(220.5–431.0)	[20]
CK (IU/L)	74.0	(51.0–112.5)	[228]	80.0†	(60.0–155.0)	[13]	184.0	(94.3–987.5)	[20]
ALD (IU/L)	4.3	(3.8–5.3)	[51]	3.9†	(3.4–5.9)	[3]	11.2	(7.5–42.3)	[17]
KL-6 (U/mL)	863.5	(477.3–1406.0)	[256]	1586.0*†	(879.5–2053.5)	[17]	742.5	(414.5–1456.3)	[20]
SP-D (ng/mL)	228	(120.8–350.8)	[210]	155.0	(109.0–310.0)	[11]	156.8	(111.3–237.0)	[16]
SP-A (ng/mL)	75.1	(48.9–109.8)	[134]	81.1	(54.5–105.0)	[9]	76.8	(51.1–94.8)	[11]
Pulmonary function test									
%VC (%)	79.8	(64.0–95.0)	[206]	63.7*	(57.6–73.8)	[14]	82.2	(66.6–88.1)	[17]
FEV1/FEV (%)	82.0	(76.1–88.1)	[206]	78.8	(73.0–87.7)	[14]	82.5	(81.8–90.4)	[17]
%DLco (%)	59.0	(41.0–74.0)	[174]	49.8	(33.8–60.5)	[13]	53.9	(41.3–66.6)	[17]
Bronchoalveolar lavage fluid									
TCC (x 10 ⁵ /mL)	2.8	(1.8–4.5)	[221]	3.3	(2.2–6.1)	[9]	3.8	(2.9–4.8)	[18]
Macrophages (%)	69.9	(52.2–80.8)	[222]	51.8	(35.6–69.0)	[9]	41.6	(29.8–57.7)	[19]
Lymphocytes (%)	11.9	(6.4–27.3)	[222]	20.4	(13.1–43.9)	[9]	36.3	(21.3–51.4)	[19]
Neutrophils (%)	6.2	(2.7–12.8)	[222]	8.4	(4.0–22.1)	[9]	7.8	(4.8–15.5)	[19]
Eosinophils (%)	3.1	(1.1–6.1)	[222]	4.0	(2.2–7.9)	[9]	7.1	(1.4–9.7)	[19]
CD4/CD8	1.7	(0.91–2.79)	[182]	0.37*	(0.19–1.32)	[9]	0.31	(0.23–0.44)	[19]

IQR; inter-quartile range, TCC; total cell count.

*; p value < 0.05 between ARS(+)IIP and ARS(–)IIP.

†; p value < 0.05 between ARS(+)IIP and ARS(+)PM/DM-ILD.

Three patients (18.8%) in the ARS(+)IIP group experienced acute exacerbations and two developed malignant neoplasms (11.1%); however, the difference was not statistically significant between the groups. Regarding the medical treatment, use of an immunosuppressive agent was more common in the ARS(+)IIP group than in the ARS(–)IIP group (50.0% vs. 20.5%, P < 0.05 by Fisher's exact test). No significant difference was observed between the groups in the percentage of patients requiring long-term oxygen therapy. The survival rates were not significantly different between the ARS(+)IIP group and the ARS(–)IIP group or the ARS(+)PM/DM-ILD group (P = 1.000 and P = 0.218, respectively; Fig. 1).

4. Discussion

This study aimed to clarify the clinical characteristics of patients with anti-ARS antibody-positive IIPs (ARS(+)IIP) by comparing them with patients with IIPs without anti-ARS antibodies (ARS(–)IIP) or PM/DM-ILD with anti-ARS antibodies (ARS(+)PM/DM-ILD). This is the first study comparing these three groups.

Anti-ARS antibodies were positive in 6.0% of patients with IIPs in the present study, similar to those in previous studies that reported a prevalence of 6.6–10.7% [11,12]. Regarding the specificity of anti-ARS antibodies, anti-KS and anti-Jo-1 were the most frequent followed by anti-EJ in the ARS(+)IIP group. In patients with ARS(+)PM/DM-ILD, anti-Jo-1 antibodies were the most frequent, as generally described in the literature, followed by anti-PL-7 antibodies [22]. Although the differences between the groups were not statistically significant, prevalence of anti-KS was higher in ARS(+)IIP vs ARS(+)PM/DM-ILD (27.8% vs 10%) consistent with previous reports [12,23–25]. These findings suggest that anti-KS antibodies are more frequently associated with ILD without myositis, while other anti-ARS antibodies are more common in PM/DM with ILD. Patients with ARS(+)IIP were significantly older and the men/women ratio was higher than that in the ARS(+)PM/DM-ILD group in the present study. These findings are also consistent with data reported in the previous studies [11,13,26]. The bias in our cohort such as recruitment from a respiratory department as well as geographical and ethnic differences may influence these results.

Table 6
Clinical course.

	ARS(–)IIP (N = 284)			ARS(+)IIP (N = 18)			ARS(+)PM/DM-ILD (N = 20)		
	% or No.	(IQR)	[n]	% or No.	(IQR)	[n]	% or No.	(IQR)	[n]
Observation period (months)	7	(0.0–28.8)	[284]	12†	(1.0–37.0)	[18]	55	(32.0–75.0)	[20]
Acute exacerbation (%)	9.6		[270]	18.8		[16]	0.0		[20]
Complication									
Malignant neoplasm (%)	22.0		[282]	11.1		[18]	20.0		[20]
Treatment									
Prednisolone (%)	55.1		[276]	77.8		[18]	100.0		[20]
Methyl-prednisolone pulse (%)	16.3		[276]	27.8		[18]	35.0		[20]
Immunosuppressants (%)	20.5		[278]	50.0*		[18]	85.0		[20]
Anti-fibrotic agents (%)	12.2		[276]	18.8		[18]	5.0		[20]
Long term oxygen therapy (%)	10.1		[278]	22.2		[18]	10.0		[20]

IQR; inter-quartile range.
*: p value < 0.05 between ARS(+)IIP and ARS(–)IIP.
†: p value < 0.05 between ARS(+)IIP and ARS(+)PM/DM-ILD.

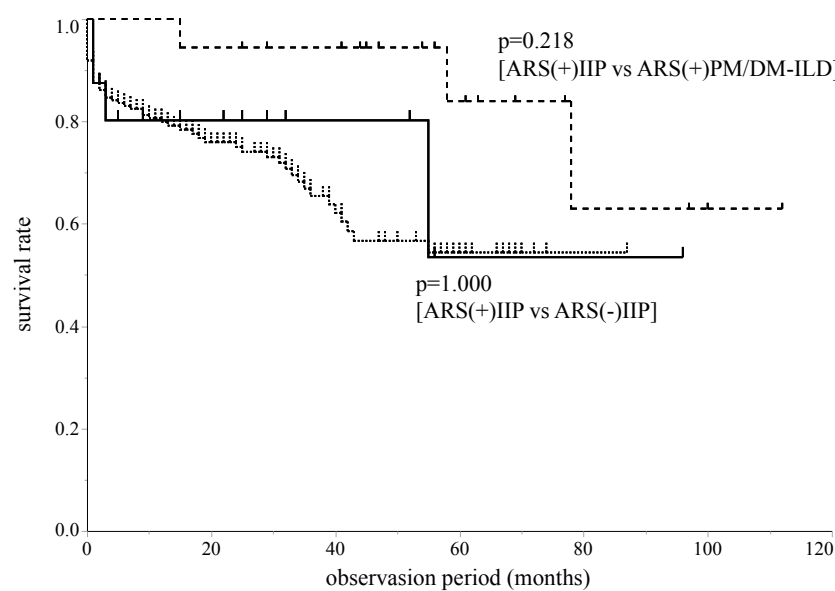


Fig. 1. Kaplan-Meier survival rates. Kaplan-Meier curves comparing the survival rates of patients with idiopathic interstitial pneumonia without anti-aminoacyl-tRNA synthetase antibodies (ARS(–)IIP, dotted line), idiopathic interstitial pneumonia with anti-aminoacyl-tRNA synthetase antibodies (ARS(+)IIP, solid line), and polymyositis- and dermatomyositis-associated interstitial lung disease with anti-aminoacyl-tRNA synthetase antibodies (ARS(+)PM/DM-ILD, dashed line) are shown.

Mechanic's hands were more frequent in the ARS(+)IIP group than in the ARS(–)IIP group, although less frequent than ARS(+)PM/DM-ILD group. “Mechanic's hands” is one of the characteristic features of ASS [10]. Although mechanic's hands were not seen in most cases of ARS(+)IIP, our results support the idea that patients with IIP are more likely to have anti-ARS antibodies if they have this sign.

It is known that patients with anti-ARS antibody-positive ILD usually have a chronic clinical course, NSIP and/or OP patterns in pulmonary CT, and a good response to corticosteroid treatment [27,28]. In the present study, NSIP was the most frequently observed pattern in patients with anti-ARS antibodies regardless of the presence of PM/DM. BALF findings showed lymphocytosis with low CD4/CD8 ratios in the ARS(+)IIP group, similar to the ARS(+)PM/DM-ILD group and consistent with previous reports [11,26], suggesting that these two disease categories have similar pathogenesis. However, UIP and DAD patterns were observed in the ARS(+)IIP group but not in the ARS(+)PM/DM-ILD group. Differences in HRCT findings such as ground-glass attenuation, consolidation and honeycombing indicated differences in HRCT pattern. It is considered that patients with a UIP pattern have a chronic but progressive clinical course, whereas those with a DAD pattern have a rapidly progressive course in IIPs [2]. Furthermore, KL-6, one of the activity markers of interstitial pneumonias, was higher and the %VC was lower in the ARS(+)IIP group. In addition, the frequency

of acute exacerbation and induction of long-term oxygen therapy appeared to be higher in the ARS(+)IIP group compared with both the ARS(–)IIP and ARS(+)PM/DM-ILD groups, though without statistical significance. These findings suggest that the ARS(+)IIP group might have more severe pulmonary involvement compared with the ARS(+)PM/DM-ILD group, although the difference in the pathogenesis remains unknown. The clinical features found in patients with various anti-ARS antibodies is called ASS based on the idea that they are similar regardless of the fine specificities of anti-ARS antibodies. However, recent studies suggested differences in the clinical features of patients with different anti-ARS antibodies; ILD in patients with non-Jo-1 anti-ARS is more severe and resistant to treatment compared with that in patients with anti-Jo-1 [29–31]. Since the percentages of different anti-ARS antibodies were different between the anti-ARS(+)IIP and ARS(+)PM/DM-ILD groups, it may reflect differences in ILD associated with different anti-ARS antibodies between these two groups.

The present study has several limitations. First, it was difficult to divide the patients into the ARS(+)IIP and ARS(+)PM/DM-ILD groups in some cases. It is well known that ILD can precede the development of myositis in some patients with PM/DM; thus, some patients in the ARS(+)IIP group might develop PM/DM if not treated promptly [19,32,33]. Additionally, the small patient cohort limits the clinical application of these findings; thus, a larger patient population should be

examined using a prospective study model in future investigations.

5. Conclusions

In conclusion, the present study demonstrated anti-ARS antibodies in 6% of patients with IIPs. Characteristics of pulmonary involvement were similar between the anti-ARS(+)IIP and ARS(+)PM/DM-ILD groups; however, some differences including HRCT findings and severe activity in pulmonary involvement were observed. Further prospective studies with a larger cohort will help elucidate the exact role of anti-ARS antibodies in IIPs.

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Conflict of interest statements

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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